Minutes of Meeting

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee

February 20, 2008

Attendees: Chairman Dr. Joseph Thomas, Dr. Michael Angelini (via teleconference), Ms. Sheri Lynn Boston, Dr. Lucy Culpepper, Dr. Nan Ferris, Dr. Michelle S. Freeman, Dr. James Gagnon, Ms. Vicki Little Faulk, Dr. Kelli Littlejohn, Mr. Ben Main, Dr. Robert Moon, Dr. Nancy J. Sawyer, and Dr. Chivers R. Woodruff

Absent: Dr. Gerard J. Ferris

1. OPENING REMARKS

Vice-chairman Main called the Pharmacy and Therapeutics (P&T) Committee Meeting to order at 9:00 a.m.

2. APPROVAL OF MINUTES

Vice-chairman Main asked if there were any corrections to the minutes from the November 14, 2007 P&T Committee Meeting. Since there were no corrections, a motion was made and seconded to approve the minutes.

3. PHARMACY PROGRAM UPDATE

Dr. Littlejohn announced that on January 1, 2008, the agency implemented the five-brand prescription limit and that all other restrictions and allowances that were in place with the four-brand limit are still in affect. She also noted that on Friday evening, February 22, 2008, Medicaid would begin the conversion process to the new Medicaid Claims Payment System. This conversion process will be completed by 8 a.m. on Monday, February 25, 2008, with eligibility checks still being available during this conversion time.

Beginning April 1, 2008, any outpatient non-electronic prescription will be required to be written on a Tamper Resistant Prescription Pad. More information concerning this can be found on the Agency's web site. Dr. Littlejohn announced that the agency is currently in the Request for Proposal process for vendors for a cost of dispensing survey and a new State Maximum Allowed Cost (SMAC) program. More information concerning this can be found on the Agency's web site.

The P&T Reference document was reviewed. Dr. Littlejohn noted that this document will continuously be in the clinical binders and should be used by the P&T Committee Members as a reference to answer any questions they may have concerning the policy and procedures, as well as their charge. It was also noted that recommendations made and/or voted on during the P&T Committee Meeting should be made using sound clinical evidence. Once the vote is completed the recommendations will be passed on to the Commissioner for review and approval.

Dr. Littlejohn noted that the Policy and Procedures of the P&T Committee were updated in December of 2007. She announced that as part of the revisions the oral presenters for a therapeutic agent under review will be required to disclose their financial relationship (if any) to the manufacturer for whom they represent. It was noted that this will not take away from the five minutes that is allocated for each presentation.

4. ORAL PRESENTATIONS BY MANUFACTURERS/MANUFACTURERS' REPRESENTATIVES

Five-minute verbal presentations were made on behalf of some pharmaceutical manufacturers. Dr. Littlejohn explained the process and timing system for the manufacturers' oral presentations. The drugs and corresponding manufacturers are listed below with the appropriate therapeutic class. There were a total of eight manufacturers' verbal presentations at the meeting.

5. PHARMACOTHERAPY CLASS REVIEWS (Please refer to the web site for full text reviews.)
The pharmacotherapy reviews began at approximately 9:10 a.m.

Estrogens American Hospital Formulary Service (AHFS) 681604
Manufacturer comments on behalf of these products:
None

Dr. Gagnon noted that the estrogens were previously reviewed in August of 2006. For many women with postmenopausal symptoms, hormone therapy (HT), which is the use of estrogens with or without a progestin, is an effective treatment; however, for many others it is not necessary. For those women who are appropriate candidates for HT, estrogen alone is used in those who have undergone a hysterectomy. A progestin is added to the HT regimen for women with a uterus, as this substantially reduces the risks of endometrial hyperplasia and endometrial cancer associated with long-term estrogen therapy. The progestin can be administered continuously or sequentially. It was noted that since the last review, a few new estradiol gel products have been added to the market, as well as a new product containing the combination of estradiol and drospirenone.

Current treatment guidelines that incorporate the estrogens were reviewed. Most guidelines currently recommend using HT to treat menopausal symptoms only, and at the lowest effective dose, for the shortest duration of treatment, while individualizing therapy and weighing the benefits versus the risks. HT is not recommended for the prevention of coronary heart disease or (routine prevention of) osteoporosis.

The Food and Drug Administration (FDA)-approved indications for the estrogens were reviewed, and it was noted that these agents have a variety of indications with the vast majority of these agents holding an approval for the treatment of menopausal symptoms.

It was noted that the pharmacokinetics of these agents vary according to their route of administration and that there are no significant differences in the adverse reactions among agents within the same dosage form and there are small differences between the different dosage forms. These differences are expected as the oral estrogens undergo a first-pass metabolism by the liver, while transdermal estrogens do not. Lower doses of estrogens are effective with transdermal formulations because inactivation and metabolism by the liver are reduced. Higher levels of estrogens from oral formulations may cause more hepatic or gastrointestinal side effects; however, the transdermal products are associated with more skin reactions.

Key pivotal trials evaluating the safety and effectiveness of the estrogens were summarized. Both the single and combination estrogen products are available in various formulations. A scientific review by Nelson et al that included 32 trials showed no significant difference in efficacy, as measured by relief of hot flashes, between conjugated equine estrogens, oral estradiol, and transdermal estradiol.

Like the single entity estrogens, the combination products are available in oral and transdermal formulations and can be administered continuously or sequentially. All estrogen and progestin combination products have been shown to be effective for the treatment of symptoms associated with menopause.

The recommendations for the use of postmenopausal hormone replacement therapy have changed since the

Women's Health Initiative study, which showed an increased risk of stroke, blood clots, invasive breast cancers and gallbladder disease and no impact on cardiac disease prevention. However, estrogens still remain the most effective treatment for the relief of menopausal symptoms and a therapeutic option for the prevention and treatment of osteoporosis in high-risk women. Currently estrogens are available in a variety of dosage forms and are available generically. The estrogen combination products are available as an oral tablet or transdermal patch. None of the combination products are available generically but some of their components are available generically.

All estrogen products (single and combination) have been shown to be effective for the treatment of symptoms associated with menopause. Specific drug therapy selection should be individualized.

Therefore, all brand estrogen products are comparable to each other and to the generics and over-the-counter (OTC) products in this class and offer no significant clinical advantage over other alternatives in general use.

No brand estrogen is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

There were no further discussions on the agents in this class. Vice-chairman Main asked the P&T Committee Members to mark their ballots.

Alpha-Glucosidase Inhibitors AHFS 682002
Manufacturer comments on behalf of these products:
None

Dr. Gagnon noted that the α-glucosidase inhibitors were previously reviewed in August 2006. Since that review, no new products have been added to the market and there are no generic formulations available in this class. The α-glucosidase inhibitors are FDA-approved for the treatment of type 2 diabetes mellitus as monotherapy or in combination with other antidiabetic medications. They work by delaying the absorption of carbohydrates from the small intestine; therefore, they have a lowering effect on postprandial blood glucose and insulin levels. The α-glucosidase inhibitors are less potent than the sulfonylureas and metformin in lowering glycosylated hemoglobin A1c (HbA_{1c}).

Current treatment guidelines addressing the use of the α-glucosidase inhibitors in Type 2 diabetes mellitus were discussed. Currently the American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) recommend metformin, along with lifestyle interventions, as initial pharmacologic therapy. The ADA/EASD do not include α-glucosidase inhibitors in their treatment algorithm due to their generally lower overall glucose-lowering effectiveness and limited clinical data. This guideline did note that these agents may be appropriate in selected patients. The American Association of Clinical Endocrinologists (AACE) and American College of Endocrinologists (ACE) guidelines list the α-glucosidase inhibitors as an initial treatment option (along with other agents) as monotherapy or combination therapy depending on the severity of disease. These guidelines do not designate a first-line agent. Additional guidelines recommend α-glucosidase inhibitors as an alternative agent after metformin and sulfonylureas. The guidelines do not give preference to one α-glucosidase inhibitor versus another.

Dr. Gagnon mentioned that the majority of adverse drug events associated with the α-glucosidase inhibitors are related to the gastrointestinal tract.

Clinical studies evaluating the safety and efficacy of the α-glucosidase inhibitors were summarized. More studies have been conducted with acarbose. In placebo-controlled studies, acarbose demonstrated significant positive effects on HbA_{1c} and 1-hour postprandial glucose levels. Significant positive changes were seen with HbA_{1c} and postprandial glucose levels when acarbose or miglitol were compared with other antidiabetic agents. Chiasson et al reported acarbose therapy was associated with a 49% relative risk reduction and 2.5% absolute risk reduction in the development of any cardiovascular event. Dr. Gagnon discussed a Cochrane review by van de Laar et al that evaluated the effects of α-glucosidase inhibitors on morbidity and mortality. Although very few studies were evaluated no differences were cited between acarbose and miglitol with regards to their effect on morbidity and mortality.

The α-glucosidase inhibitors are approved for the treatment of type 2 diabetes mellitus as monotherapy or in combination with other antidiabetic agents. The effectiveness of these agents has been demonstrated through clinical trials; however, there are no head-to-head trials comparing these agents to each other.

Acarbose and miglitol share similar gastrointestinal adverse drug events including abdominal pain, diarrhea, and flatulence. There are very few drug-to-drug interactions with these agents and they share the same dosing schedule.

Currently the ACE/ACCE treatment guidelines for type 2 diabetes mellitus do not designate a first-line therapy and state that in patients naïve to therapy, α-glucosidase inhibitors are among the preferred and recommended therapies, but no preference for one α-glucosidase inhibitor over the other is made. Other national and international guidelines indicate that α-glucosidase inhibitors may be considered a further option for the treatment of type 2 diabetes mellitus after designated first-line therapies such as metformin and sulfonylureas have failed or are not tolerated.

Therefore, all brand products within the class reviewed are comparable to each other and to the generics and OTC products in this class and offer no significant clinical advantage over other alternatives in general use.

No brand α-glucosidase inhibitor is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

Dr. Moon inquired if it was known why miglitol was not available in the United Kingdom. Dr. Gagnon replied that this information had not been obtained. Vice-chair Main reminded P&T Committee Members that all of these reviews are re-reviews; however, the recommendations may have changed. There were no further discussions on the agents in this class. Vice-chairman Main asked the P&T Committee Members to mark their ballots.

Amylinomimetics AHFS 682003

Manufacturer comments on behalf of these products:

None

Dr. Gagnon noted that the amylinomimetics were last reviewed in November 2006 as part of the review entitled the Single Entity Miscellaneous Antidiabetic Agents. Since the last review pramlintide was assigned to a separate American Hospital Formulary Service (AHFS) class. The only medication in the class of agents known as the amylinomimetics is pramlintide. Pramlintide is a synthetic analog of the human hormone amylin. Amylin affects blood glucose by delaying gastric emptying, suppressing postprandial glucagon secretion subsequently preventing glucose release from the liver, and decreasing calorie intake through central

mediation of appetite. A pen device has become available since the last review and there are no generic formulations available.

The role of pramlintide in national and international guidelines was discussed. Currently the ADA/EASD recommends metformin, along with lifestyle interventions, as initial pharmacologic therapy for the treatment of type 2 diabetes mellitus. The ADA/EASD did not include pramlintide in their treatment algorithm due to their generally lower overall glucose-lowering effectiveness and limited clinical data. This guideline did note that these agents may be appropriate in selected patients. The AACE and ACE guidelines state that in patients with an HbA_{1c} of 6.5%-8.5%, an amylin analog such as pramlintide, in combination with prandial insulin may be used to achieve glycemic goals. The Institute for Clinical Systems Improvement (ICSI) recommends that an amylin analog should only be considered in patients with insulin-using type 2 or type 1 diabetes mellitus who have failed to achieve adequate glycemic control despite individualized insulin management and are receiving ongoing care under the guidance of a health care professional skilled in the use of insulin.

Dr. Gagnon noted that pramlintide is approved for the treatment of type 1 and type 2 diabetes mellitus but must be given concomitantly with insulin.

The majority of adverse events documented with pramlintide are gastrointestinal in nature. In addition when used in conjunction with insulin, pramlintide can increase the risk of insulin-induced hypoglycemia particularly in type 1 diabetics. This risk has led to a black box warning and in order to minimize the risk, the manufacturer has recommended that certain patients should not be considered for pramlintide therapy.

Clinical trials show that when compared to placebo, pramlintide decreases HbA_{1c} to a greater extent than placebo in patients with type 1 or type 2 diabetes mellitus who are already receiving insulin. In addition, pramlintide was associated with reductions in insulin use and appears to promote weight loss.

Currently, the use of pramlintide is addressed in a few consensus treatment guidelines and is typically recommended to be used as adjunctive therapy to mealtime insulin in patients who are not controlled on insulin.

Though pramlintide itself does not cause hypoglycemia, in clinical trials an increased risk of serious hypoglycemic episodes was observed. To minimize this risk, patients must be carefully selected, proper patient education must be provided and glucose levels and insulin doses must be carefully monitored. In addition, pramlintide can potentially be used off label, such as for weight loss in nondiabetic patients and for management of diabetes in patients not currently using insulin. To minimize both off-label use and the risk of severe hypoglycemia, pramlintide should be reserved for use in diabetic patients, following careful screening, who have not achieved adequate glycemic control with insulin therapy.

Therefore, all brand products within the class review are comparable to each other and to the generics and OTC products in this class and offer no significant clinical advantage over other alternatives in general use. Since this agent is only indicated for adjunctive therapy, it is advisable that it be managed through the existing medical justification portion of the prior-authorization process.

No brand amylinomimetic is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred agents.

Dr. Sawyer inquired how common is the use of pramlintide. Dr. Gagnon replied that the exact number of patients utilizing this agent is not known; however, the use of this agent is limited to specific patient populations, such as patients who are not adequately controlled on insulin alone. Dr. Woodruff inquired how many doses of pramlintide were prescribed for Medicaid patients in the past year. Dr. Littlejohn replied that they do not have that information readily available but could obtain it. There were no further discussions on the agents in this class. Vice-chairman Main asked the P&T Committee Members to mark their ballots.

Biguanides AHFS 682004
Manufacturer comments on behalf of these products:
None

Dr. Ferris began the clinical presentation by stating that the biguanides were previously reviewed in August 2006 and metformin is the only chemical entity in this class. Metformin improves glucose tolerance in patients with type 2 diabetes by lowering both basal and postprandial plasma glucose. Metformin is available generically in both an immediate-release and sustained-release tablet. The oral solution (Riomet®) does not have a generic formulation.

Treatment guidelines incorporating the biguanides were discussed. Most national and international organizations, including the ADA and the EASD, recommend metformin, along with lifestyle intervention, as the initial pharmacologic therapy for the management of type 2 diabetes, in the absence of specific contraindications, when lifestyle intervention fails to achieve or maintain metabolic goals. Recommendations by the AACE and ACE are more detailed and encompass more treatment options. In these guidelines, metformin is still considered a first-line treatment option either as monotherapy or combination therapy along with other antihyperglycemic agents. The immediate-release tablets and solution are FDA approved for patients who are 10 years of age and older, while the extended-release products are approved for patients at least 17 years of age.

The rate and extent of absorption of metformin oral solution (Riomet®) was found to be bioequivalent to that of metformin tablets (Glucophage®). Gastrointestinal side effects (diarrhea and nausea) are the most frequent adverse reactions with metformin and may occur more frequently with the immediate-release formulations. Other adverse events appear to be comparable among the various dosage forms. The black box warning regarding metformin and lactic acidosis, a rare but serious metabolic complication, was mentioned.

Overall, the extended-release products have been shown to be comparable to the immediate-release formulations in reducing HbA_{1c} and improving fasting plasma glucose concentrations. The meta-analysis comparing metformin to other antidiabetic agents or placebo by Saenz et al was discussed. In this meta-analysis, obese patients that received metformin showed a more significant benefit than sulfonylureas or insulin for any diabetes-related outcome and for all-cause mortality.

In conclusion, the biguanides are approved for the treatment of type 2 diabetes and their effectiveness as monotherapy and in combination with other oral antidiabetic agents and/or insulin has been demonstrated through many clinical trials. Metformin is available in several different formulations, and generic formulations are available for the immediate-release and sustained-release tablets. There are no studies that have demonstrated that one brand is safer or more efficacious than another.

Therefore, all brand products within the class reviewed are comparable to each other and to the generics and OTC products in this class and offer no significant clinical advantage over other alternatives in general use.

No brand biguanide is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

Dr. Sawyer inquired if Medicaid would approve the use of metformin for polycystic ovarian syndrome. Dr. Ferris replied that there are currently no restrictions for the indications of the generic formulations of metformin. There were no further discussions on the agents in this class. Chairman Thomas asked the P&T Committee Members to mark their ballots.

Dipeptidyl Peptidase-4 (DPP-4) Inhibitors Single Entity Agents AHFS 682005
Manufacturer comments on behalf of these products:
Januvia® (sitagliptin)-Merck

Dr. Littlejohn stopped the speaker and reminded her that no cost or financial information can be presented to the P&T Committee Members, and to please utilize the oral presentation summary that had been approved for presentation.

Dr. Gagnon noted that the dipeptidyl peptidase-4 (DPP-4) inhibitors represent a new class of oral antidiabetic medications. This class reversibly blocks the inactivation of incretin hormones resulting in an increase in insulin production and release from pancreatic β cells and a decrease in glucagon secretion from pancreatic α cells, thus decreasing hepatic glucose production. Gastric emptying is also delayed. DPP-4 inhibitors primarily target postprandial glucose and have also been shown to decrease fasting plasma glucose levels. Sitagliptin is currently the only DPP-4 inhibitor available in the United States (US). Sitagliptin was FDA approved in October 2006 as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus, either alone or in combination with other oral antihyperglycemic agents.

The role of sitagliptin in a few national and international treatment guidelines was discussed. Since this product was approved in 2006, guidelines published or completed before then have not incorporated this agent. The ADA/EASD guideline recommends metformin, along with lifestyle interventions, as initial pharmacologic therapy for the treatment of type 2 diabetes. The ADA/EASD did not include sitagliptin in their treatment algorithm due to its generally lower overall glucose-lowering effectiveness and limited clinical data. This guideline did note that this agent may be appropriate in selected patients. The AACE and ACE guidelines list the DPP-4 inhibitors as an initial treatment option (along with other agents) either alone or in combination with other agents depending on the severity of disease. However, these guidelines do not designate a first-line agent.

The majority of adverse events documented with sitagliptin are mild. In addition to these documented adverse events there is an increased risk of hypoglycemia when sitagliptin is given in combination with a sulfonylurea and a lower dose of the sulfonylurea may be required. There have also been postmarketing reports of hypersensitivity reactions including anaphylaxis, angioedema and exfoliative skin reactions such as Stevens-Johnson syndrome.

Clinical studies evaluating the safety and efficacy of the single entity DPP-4 inhibitors were discussed. In a number of randomized-controlled studies, sitagliptin monotherapy demonstrated enhanced glycemic control, with improvements in HbA_{1c}, fasting plasma glucose, and postprandial glucose over placebo. Studies involving sitagliptin in combination with metformin or pioglitazone have demonstrated an additive effect in glycemic control. In a trial monitoring the change in HbA_{1c} from baseline, sitagliptin was determined to be as effective as glipizide. A systematic review of incretin therapy in type 2 diabetes showed that DPP-4 inhibitors demonstrated a small increase in weight as compared to placebo and provided a decrease in body weight

compared to an increase with glipizide. The long-term safety and efficacy of these agents have yet to be established and the use of sitagliptin in addition to insulin has not yet been studied.

In summary, the AACE medical guidelines for clinical practice for the management of diabetes mellitus do not designate a first-line therapy for the treatment of type 2 diabetes mellitus, but do include sitagliptin among the recommended therapeutic choices. The ACE/AACE Diabetes Road Map Task Force: Road Maps to Achieve Glycemic Control in Type 2 Diabetes designate DPP-4 inhibitors as one of the preferred oral antidiabetic agents for patients. ADA/EASD guideline states that sitagliptin, as well as other agents, were not included in the treatment algorithm due to their generally lower overall glucose-lowering effectiveness and limited clinical data. However, these agents may be appropriate in selected patients.

Therefore, all brand products in this class review are comparable to the generics and OTC products in this class and offer no significant clinical advantage over other alternatives in general use.

No brand single entity dipeptidyl peptidase-4 (DPP-4) inhibitor is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

There were no further discussions on the agents in this class. Chairman Thomas asked the P&T Committee Members to mark their ballots.

Dipeptidyl Peptidase-4 (DPP-4) Inhibitors Combination Products AHFS 682005
Manufacturer comments on behalf of these products:
Janumet® (sitagliptin and metformin)-Merck

Dr. Gagnon noted that there is one combination DDP-4 product available, sitagliptin and metformin. This agent has been FDA approved as an adjunct to diet and exercise, to improve glycemic control in adult patients with type 2 diabetes mellitus who are not adequately controlled on metformin or sitagliptin alone or in patients already being treated with the combination of sitagliptin and metformin.

The role of sitagliptin and metformin in national and international treatment guidelines was discussed. Since this product was approved in 2006, guidelines published or completed before then have not incorporated this combination product. The ADA/EASD does not discuss the role of the combination DPP-4 inhibitors in the treatment of type 2 diabetes but does recommend metformin, along with lifestyle interventions, as initial pharmacologic therapy for the treatment of type 2 diabetes and notes that sitagliptin was not included in the treatment algorithm due to its generally lower overall glucose-lowering effectiveness and limited clinical data. The AACE and ACE guidelines recommend that in patients with an HbA_{1c} of 7%-8% combination therapy should be initiated and that regimens may include a DPP-4 inhibitor combined with metformin or a thiazolidinedione although this guideline does not designate a first-line agent.

The majority of adverse events reported with the combination DPP-4 inhibitors are gastrointestinal in nature. Since the combination product contains metformin as one of its components, the product is contraindicated in certain patient populations.

Clinical studies evaluating the safety and efficacy of the combination DPP-4 inhibitors were discussed. These trials have demonstrated an additive effect in glycemic control for the combination of sitagliptin and metformin when compared to either agent alone or placebo. These results are supported by significant differences in HbA_{1c} and fasting plasma glucose in favor of the combination regimen. There are no published

trials available to date that assess the fixed-dose combination product. Additionally, the long-term safety and efficacy of this combination product has yet to be established.

The combination of sitagliptin, a DPP-4 inhibitor, with a fixed dose of metformin, a biguanide, is the only DPP-4 inhibitor combination product currently available in the US. The components of the fixed-dose combination product are available in separate formulations and only metformin is available generically.

In summary, the AACE treatment guidelines for clinical practice for the management of diabetes mellitus do not designate a first-line therapy for the treatment of type 2 diabetes mellitus, but do include sitagliptin among the recommended therapeutic choices. The ACE/AACE Diabetes Road Map Task Force: Road Maps to Achieve Glycemic Control in Type 2 Diabetes designate DPP-4 inhibitors, as well as other oral agents, as preferred oral antidiabetic agents for patients. The updated ADA/EASD states that sitagliptin as well as other agents, were not included in the treatment algorithm due to their generally lower overall glucose-lowering effectiveness and limited clinical data. However, these agents may be appropriate in selected patients. It is important to note that the role of the combination sitagliptin and metformin agent was not specifically discussed in any of the treatment guidelines.

Therefore, all brand products in this class review are comparable to the generics and OTC products in this class and offer no significant clinical advantage over other alternatives in general use.

No brand combination dipeptidyl peptidase-4 (DPP-4) inhibitor is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

There were no further discussions on the agents in this class. Chairman Thomas asked the P&T Committee Members to mark their ballots.

Incretin Mimetics AHFS 682006
Manufacturer comments on behalf of these products:
None

Dr. Gagnon noted that the incretin mimetics were last reviewed in November 2006 as part of the review entitled the Single Entity Miscellaneous Antidiabetic Agents. Since the last review exenatide was assigned to a separate AHFS class. The only medication in the class of agents known as the incretin mimetics is exenatide. Exenatide binds to and activates glucagon-like peptide-1 (GLP-1) receptors in the body resulting in enhanced glucose-dependent insulin secretion, suppressed glucagon secretion during periods of hyperglycemia, slowed gastric emptying, and reduced food intake. Since that review, no new products have been added to the market and there are no generic formulations available in this class.

The role of exenatide in national and international guidelines was discussed. Currently the ADA/EASD recommends metformin, along with lifestyle interventions, as initial pharmacologic therapy for the treatment of type 2 diabetes. The ADA/EASD did not include exenatide in their treatment algorithm due to their generally lower overall glucose-lowering effectiveness and limited clinical data. This guideline did note that these agents may be appropriate in selected patients. The AACE and ACE guidelines state that exenatide may be used with approved combinations of oral therapies in patients, who have not achieved glycemic goals, but it is not indicated for insulin-using patients and it is not listed as a first-line treatment option.

Dr. Gagnon noted that exenatide is approved for the adjunctive treatment in patients with type 2 diabetes mellitus who are taking metformin, a sulfonylurea, a thiazolidinedione, a combination of metformin and a sulfonylurea, or a combination of metformin and a thiazolidinedione, but have not achieved adequate glycemic control. Exenatide is not approved for the management of type 1 diabetes.

The most common adverse reactions reported with the incretin mimetics are nausea, vomiting, and hypoglycemia. Patients on exenatide may develop anti-exenatide antibodies. Patients who developed anti-exenatide antibodies had similar rates and types of adverse events.

In October 2007, the FDA published an alert regarding an association between exenatide and pancreatitis. This alert was based on a review of 30 postmarketing reports of acute pancreatitis in patients taking Byetta®. It is recommended that healthcare providers be aware of, and review with their patients the signs and symptoms of pancreatitis, including persistent severe abdominal pain which may be accompanied by nausea and vomiting. It is also recommended to discontinue Byetta® if pancreatitis is suspected.

Clinical studies evaluating the safety and efficacy of the incretin mimetics were discussed. Exenatide has not been directly compared to any oral antidiabetic treatment available for type 2 diabetes mellitus. In clinical trials, exenatide demonstrated the ability to reduce HbA_{1c} by –0.4% to –0.9% in type 2 diabetics not adequately controlled with various oral agents and/or insulin. An interim analysis demonstrated maintenance of HbA_{1c} and weight reductions for periods of up to 104 weeks. In direct-comparison trials with insulin therapy, exenatide was shown to be as effective in reducing HbA_{1c} as insulin glargine and insulin aspart. A loss of weight was observed in the exenatide-treated patients while the insulin-treated patients gained weight.

Exenatide has demonstrated effectiveness in improving glycemic control within the drug's FDA-approved indications. Exenatide has not been directly compared to oral treatments for type 2 diabetes nor has there been any published data examining the safety and efficacy of exenatide as monotherapy or in combination with meglitinides or α-glucosidase inhibitors. Exenatide also has a high incidence of gastrointestinal side effects, particularly nausea. In addition, clinical trials reported that exenatide produces weight loss which may raise concerns for off-label use for weight control.

In summary, the use of exenatide is currently addressed in a few consensus treatment guidelines and is recommended to be used as adjunctive therapy in type 2 diabetic patients who are not adequately controlled on first-line agents.

Since this agent is only indicated for adjunctive therapy, it is advisable that this agent be managed through the existing medical justification portion of the prior-authorization process.

Therefore, all brand products in this class review are comparable to the generics and OTC products in this class and offer no significant clinical advantage over other alternatives in general use.

No brand incretin mimetic is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred agents.

Dr. Woodruff inquired if there was a way to determine what percentage of patients are currently using this agent off-label for weight loss. Dr. Littlejohn replied that since this agent currently requires a prior authorization, an appropriate diagnosis would be required in order for the patient to obtain this medication, or

medical justification would have been submitted. There were no further discussions on the agents in this class. Chairman Thomas asked the P&T Committee Members to mark their ballots.

Insulin AHFS 682008

Manufacturer comments on behalf of these products:
Lantus® (insulin glargine)-Sanofi Aventis
Levemir ® (insulin detemir)-Novo Nordisk
Novolog® (insulin aspart)-Novo Nordisk
Novolog® Mix 70/30® (insulin aspart and insulin aspart protamine)-Novo Nordisk

Dr. Littlejohn stopped the speaker for Lantus® and reminded him that no anecdotal information can be presented to the P&T Committee Members, and to please utilize the oral presentation summary that had been approved for presentation.

Dr. Ferris began the clinical presentation by pointing out that all of the insulin products on the market today are either human insulin or an insulin analog. All of the rapid- and long-acting insulins are analog preparations. The human insulins are available as short- and intermediate-acting insulins and most of the injectable formulations (of human insulin) are available OTC–which means that they are on the Alabama Medicaid Preferred Drug List (PDL). Since the previous full therapeutic class review in August 2006, an inhaled human insulin formulation called Exubera® has been added to the market but the manufacturer (Pfizer) announced last October that this product would no longer be manufactured.

Treatment guidelines using the insulins for both type 1 and type 2 diabetes mellitus were discussed. The general consensus of various national and international treatment guidelines for the management of type 1 diabetes is that insulin should be individualized and intensive therapy is necessary for optimal outcomes. The ADA recommends that therapy consists of the following components: use of multiple dose insulin injections or continuous subcutaneous insulin infusion therapy; matching of prandial insulin to carbohydrate intake, premeal blood glucose and anticipated activity; and for many patients, especially if hypoglycemia is a problem, use of insulin analogs. The AACE recommends initiating intensive insulin therapy with a long-acting insulin analog in combination with a rapid-acting insulin analog or inhaled insulin at meals, or with continuous subcutaneous insulin infusion.

In type 2 diabetics, in general the use of insulin is recommended when optimal treatment with oral glucose-lowering agents and lifestyle interventions are unable to achieve or maintain blood glucose at target levels. As in type 1 diabetics, insulin regimens should be individualized. Current guidelines by the ADA do not give preference to one insulin product over another for the management of type 2 diabetes. The guidelines by the AACE and ACE, however, are more detailed and outline situations where some insulin preparations may be preferred over others.

The primary differences among the available insulin products are their onset and duration of actions. With the exception of hypoglycemia, which was discussed later in the presentation, there are no clinically significant differences in the drug interactions or adverse events.

Key pivotal clinical trials were discussed. In general, insulins with similar onset and duration of actions have demonstrated comparable reductions in HbA_{1c} levels. There are some advantages, however, of the newer insulin analogs. The newer rapid-acting insulin analogs typically have a more favorable postprandial glycemic profile compared to short-acting regular human insulin injections and some studies reported that they were more effective than regular human insulin in reducing HbA_{1c} levels. There are limited head-to-head trials

comparing the rapid-acting insulin analogs to each other. The study by Dreyer et al compared insulin glulisine to insulin lispro in type 1 diabetic patients. Both agents produced a comparable decrease in HbA_{1c}. The incidence of adverse reactions and hypoglycemic events were similar. There was a significant increase in total insulin dose with insulin lispro (+1.01 U) compared to insulin glulisine (–0.86U); however, the real clinical significance of this difference is not known. The trial by Niskanen et al compared premixed insulin aspart to insulin lispro in type 2 diabetic patients. The authors noted comparable reductions in HbA_{1c} and similar blood glucose profiles and adverse events between the two treatment groups.

Overall, the trials evaluating the long-acting insulin analogs have shown that these agents are at least as effective as NPH insulin in reducing HbA_{1c} and improving fasting plasma glucose levels but are associated with lower risks of hypoglycemia. There are limited head-to-head studies comparing the safety and efficacy of the long-acting insulin analogs (insulin detemir and glargine) to each other. The study by Pieber et al compared insulin detemir to insulin glargine, both along with prandial insulin aspart in type 1 diabetics. At 26 weeks, both groups had comparable changes in HbA_{1c}. Insulin glargine, however, resulted in significantly lower home measured fasting plasma glucose levels than insulin detemir. The overall risk of hypoglycemia was comparable in both treatment groups. However, insulin detemir resulted in lower rates of nocturnal hypoglycemia than with insulin glargine. Additional studies are needed comparing these agents to each other.

In conclusion, the Diabetes Control and Complications Trial (DCCT) and United Kingdom Prospective Diabetes Study (UKPDS) have demonstrated that intensive glycemic control with insulin significantly reduces the rate of onset and progression of diabetic complications when compared to standard therapy. Current evidence has demonstrated that the rapid-acting insulin analogs (insulin aspart, glulisine and lispro) are at least as effective as regular insulin injections in terms of HbA_{1c} reduction and have greater postprandial glycemic control than the regular insulins. In two studies comparing insulin aspart or insulin glulisine to insulin lispro, there were no significant differences in HbA_{1c} reduction, postprandial glycemic profiles, or rates of hypoglycemia. The long-acting insulin analogs (insulin detemir and glargine) have been shown to be at least as effective as NPH insulin and are associated with less hypoglycemia. There is insufficient data to determine if one long-acting insulin analog offers a significant clinical advantage over the other.

Therefore, all brand products within the class reviewed, with the exception of the rapid-acting and long-acting insulin analogs, are comparable to each other and to the generics and OTC products in this class and offer no significant clinical advantage over other alternatives in general use. For patients with inadequate postprandial glycemic control, however, at least one rapid-acting insulin analog should be available on the PDL. At least one long-acting insulin analog should be available on the preferred drug list for patients requiring basal insulin therapy.

The recommendations are for Alabama Medicaid to work with manufacturers on cost proposals so that at least one brand rapid-acting insulin analog is selected as a preferred agent. Alabama Medicaid should work with manufacturers on cost proposals so that at least one brand long-acting insulin analog is selected as a preferred agent. No brand insulin, with the exception of rapid-acting and long-acting insulin analogs, is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

Ms. Boston stated that it is very important that a basal insulin be included on the PDL. Dr. Culpepper asked that the recommendations be clarified. Dr. Ferris clarified the recommendation. There were no further discussions on the agents in this class. Chairman Thomas asked the P&T Committee Members to mark their ballots.

Meglitinides Single Entity Agents AHFS 682016
Manufacturer comments on behalf of these products:
None

Dr. Ferris noted that the meglitinides class consists of two agents, nateglinide and repaglinide. They are FDA approved as adjunct to diet and exercise either alone or in combination with metformin or a thiazolidinedione for the treatment of type 2 diabetes mellitus. Like the sulfonylureas, they stimulate the release of insulin from the pancreas and for this reason these two classes of drugs are called the insulin secretagogues. Since the previous review in August 2006, no new agents or formulations have been added to the market. There are no generic products available in this class. Currently, there is one brand meglitinide on the Alabama Medicaid PDL.

The treatment guidelines incorporating the meglitinides were discussed. Most national and international guidelines, including the ADA and the EASD recommend metformin, along with lifestyle intervention, as the initial pharmacologic therapy for the management of type 2 diabetes. The ADA and EASD do not include meglitinides, as well as other antidiabetic agents, in their treatment algorithm due to their generally lower overall glucose-lowering effectiveness and limited clinical data. This guideline did note that these agents may be appropriate in selected patients. The AACE does consider meglitinides as a first-line treatment option in selected patients. The joint ACE and AACE Diabetes Road Map, however, considers the meglitinides as an alternative for patients not able to take initial therapy. All of the guidelines include the meglitinides as a treatment option for combination therapy. The guidelines do not give preference to one meglitinide over another.

Dr. Ferris noted that there are some differences in the pharmacokinetic parameters between these agents; however, both agents have a short half-life of 1-1.5 hours and have similar dosing schedules. There are a few more drug interactions and adverse reactions reported with repaglinide than nateglinide.

Key clinical trials evaluating the safety and efficacy of the meglitinides were discussed. The study by Rosenstock et al directly compared nateglinide to repaglinide monotherapy in 150 adult patients with type 2 diabetes mellitus. Changes in HbA_{1c} values compared to baseline were significantly lower with repaglinide compared to nateglinide and more patients achieved HbA_{1c} values $\leq$7%; however, this difference was not statistically significant. The mean change from baseline in fasting plasma glucose (FPG) was greater with repaglinide than for nateglinide. There were no notable differences in adverse events for the two treatment groups with the exception of more weight gain reported with repaglinide. In the next study, Li et al also directly compared nateglinide to repaglinide (N=223). In this study, both agents significantly decreased fasting blood glucose, postprandial glucose, and HbA_{1c}. While the HbA_{1c} levels at week 12 were not significantly different, the HbA_{1c} reduction compared to baseline was significantly greater for repaglinide. There were no significant differences between the two meglitinides with regards to effect on insulin sensitivity, β-cell function, triglycerides, total cholesterol, or body mass index. While the incidence of adverse events between the groups was not statistically significant, the rate of adverse reactions was 4.5% in the repaglinide group and 0.9% in the nateglinide group. There were no significant differences in any of the secondary end points. There are no long-term safety and efficacy studies comparing these agents to each other.

In conclusion, the effectiveness of these agents as monotherapy and in combination with other oral antidiabetic agents was demonstrated through many clinical trials. From the data presented, there is no evidence available to indicate what effect meglitinides will have on important long-term outcomes. While a few short-term studies have reported repaglinide to be more effective than nateglinide, additional studies with

larger sample sizes and over longer periods of time are needed to determine if one meglitinide offers an advantage in glycemic control or safety over the other.

Therefore, all brand products within the class reviewed are comparable to each other and to the generics and OTC products in this class and offer no significant clinical advantage over other alternatives in general use.

No brand meglitinide is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

There were no further discussions on the agents in this class. Chairman Thomas asked the P&T Committee Members to mark their ballots.

Sulfonylureas Single Entity Agents AHFS 682020
Manufacturer comments on behalf of these products:
None

Dr. Ferris stated that the sulfonylureas were previously reviewed in August 2006. Since the last review, there have been no significant additions to this class in the form of new brand or generic entities. All products reviewed in this class are available in a generic formulation.

The treatment guidelines using the single entity sulfonylureas were discussed. In general, the national and international diabetes treatment guidelines recommend metformin, along with lifestyle intervention, as the initial pharmacologic therapy for the management of type 2 diabetes. The AACE does consider sulfonylureas as a first-line treatment option in selected patients. The joint ACE and AACE Diabetes Road Map, however, considers sulfonylureas as an alternative for patients not able to take initial therapy. All of the guidelines include the sulfonylureas as a treatment option for combination therapy. The guidelines do not give preference to one sulfonylurea over another.

While there may be some differences in the pharmacokinetic parameters of the sulfonylureas, all of the agents in this class are available in a formulation where they can be dosed once a day. There are no significant differences among these agents with regards to drug interactions or adverse events. The sulfonylureas carry a warning regarding an increased risk of cardiovascular mortality when compared to treatment with diet alone or diet plus insulin. This warning was based on the study conducted by the University Group Diabetes Program (UGDP). It is important to note that tolbutamide was the only sulfonylurea in this study.

The clinical studies presented in the effectiveness section demonstrate that the sulfonylureas are equally effective when administered in equipotent doses and that they have comparable glycemic control.

In summary, the single entity sulfonylureas are FDA approved and effective for the treatment of type 2 diabetes. All of them are available generically. Therefore, all brand products within the class reviewed are comparable to each other and to the generics and OTC products in this class and offer no significant clinical advantage over other alternatives in general use.

No brand single entity sulfonylurea is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

There were no further discussions on the agents in this class. Chairman Thomas asked the P&T Committee Members to mark their ballots.

Sulfonylureas Combination Products AHFS 682020
Manufacturer comments on behalf of these products:
None

Dr. Ferris noted that since the last review, there have been no significant additions. Both sulfonylurea combination agents contain metformin as one of the components and both agents are available generically. Both combination products are approved for use as initial therapy or when initial therapy with a sulfonylurea or metformin does not result in adequate glycemic control. The fixed-dose combination glyburide and metformin is also indicated for combination therapy with a thiazolidinedione.

While all of the guidelines include the sulfonylureas as a treatment option for combination therapy, only the guideline by the AACE addressed the use of fixed-dose combination products. For patients who are naïve to pharmacologic therapy and have an HbA_{1c} of 7%-8%, combination therapy is recommended. Regimens may include a secretagogue (or sulfonylurea) with metformin either as concurrent therapy or a fixed-dose regimen.

There are no significant differences in the pharmacokinetics, drug interactions, or adverse drug events for these two combination products. Both products contain the black box warning for metformin and lactic acidosis.

A majority of the clinical trials compared combination sulfonylurea therapy to treatment with a single agent. In each trial, combination therapy was found to significantly increase glycemic control. Trials investigating the impact of dose simplification reported that the use of the fixed-dose combination product significantly increased adherence. Only one study evaluated the clinical impact of increased adherence and found that the fixed-dose combination product was associated with a significantly greater decrease in HbA_{1c}. This was a retrospective analysis of pharmacy and laboratory claims. Additional prospective head-to-head trials are needed to compare the efficacy and safety of fixed-dose combination products to concurrent administration of the separate components.

In summary, the combination sulfonylureas are approved for the treatment of type 2 diabetes and the effectiveness of these products was demonstrated through clinical trials. Both products reviewed are available generically. Therefore, all brand products within the class reviewed are comparable to each other and to the generics and OTC products in this class and offer no significant clinical advantage over other alternatives in general use.

No brand combination sulfonylurea is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

There were no further discussions on the agents in this class. Chairman Thomas asked the P&T Committee Members to mark their ballots.

Thiazolidinediones Single Entity Agents AHFS 682028
Manufacturer comments on behalf of these products:
Actos® (pioglitazone)-Takeda

Dr. Ferris noted that the thiazolidinediones were previously reviewed in August 2006. There are 2 single entity thiazolidinediones currently on the market and they are pioglitazone and rosiglitazone. There are no generic formulations in this class and both brands are currently on the Alabama Medicaid PDL. Since the previous review, the most significant changes in this class have been the addition of a black box warning regarding congestive heart failure for both agents, and the addition of a black box warning regarding myocardial ischemia for rosiglitazone.

The current treatment guidelines using the single entity thiazolidinediones were discussed. Most national and international organizations, including the ADA and the EASD, recommend metformin, along with lifestyle intervention, as the initial pharmacologic therapy for patients with type 2 diabetes. In January 2008, the ADA/EASD issued an update to their algorithm regarding the thiazolidinediones. They stated that thiazolidinediones along with sulfonylureas and insulin remain the recommended treatment options that should be added to metformin and lifestyle modifications if target HbA_{1c} levels are not achieved. However, greater caution should be exercised prior to selecting a thiazolidinedione, especially in patients at risk of, or with, congestive heart failure. They do note potential disadvantages of thiazolidinediones include fluid retention, twofold increased risk of congestive heart failure and weight gain. They also note that rosiglitazone may potentially increase the risk of myocardial infarction and has an atherogenic lipid profile. The update also notes that pioglitazone may potentially decrease the risk of myocardial infarction and has an improved lipid profile. Guidelines endorsed by the AACE and ACE consider thiazolidinediones as an initial treatment option, along with metformin and other agents, either as monotherapy or combination therapy based upon the patient's HbA_{1c} levels. The AACE and ACE guidelines do not give preference to one thiazolidinedione over another but the road map cites a report that suggests a possible link of rosiglitazone to cardiovascular events that requires further evaluation. The remainder of the guidelines in the review (by the International Diabetes Federation, ICSI and National Institute for Health and Clinical Excellence) recommend metformin as the first-line agent for the management of type 2 diabetes. Dr. Ferris mentioned that the only difference between the two agents with regards to FDA-approved indications is that rosiglitazone is not approved for combination therapy with insulin.

Dr. Ferris pointed out that in May 2007, the FDA issued an alert informing healthcare professionals of a potential safety concern related to rosiglitazone. Safety data from a pooled analysis of controlled clinical trials noted a significant increased risk of myocardial infarction and cardiovascular-related deaths in patients taking rosiglitazone; however, other published and unpublished data from long-term clinical trials provided contradictory evidence. In July 2007, the FDA met and determined that rosiglitazone could remain on the market with a black box warning regarding its cardiovascular risk. At this time, pioglitazone has not been associated with an increased risk of myocardial infarction and/or cardiovascular related deaths. One study (PROactive study) conducted in over 5,000 patients reported that pioglitazone was associated with a decreased risk of the composite of all-cause mortality, myocardial infarction and stroke (the main secondary end point of the study). A meta-analysis of 19 trials (Lincoff et al) encompassing over 16,000 patients also reported that the composite of death from any cause, myocardial infarction or stroke was lower with pioglitazone than placebo or an active comparator.

Dr. Ferris noted that both thiazolidinediones carry the black box warning regarding congestive heart failure. Rosiglitazone carries the black box warning regarding myocardial ischemia. Please note that the warning states "In their entirety, the available data on the risk of myocardial ischemia are inconclusive."

In addition to the cardiovascular outcomes trials already mentioned, key pivotal clinical trials for the single entity thiazolidinediones were discussed. Head-to-head trials comparing pioglitazone to rosiglitazone demonstrate that both agents produced comparable reductions in HbA_{1c}; however, differences in lipoprotein

profiles were reported. For example, the study by Goldberg et al reported that pioglitazone significantly reduced triglyceride levels and significantly increased high-density lipoprotein (HDL) cholesterol compared to rosiglitazone. There were no differences in adverse events including edema, heart failure, hypoglycemic episodes and weight gain

In conclusion, both pioglitazone and rosiglitazone are FDA approved for use as monotherapy and in combination with other antidiabetic agents to improve glycemic control in type 2 diabetes. Most national and international organizations, including the ADA and EASD, recommend metformin as the first-line therapeutic agent with thiazolidinediones and sulfonylureas as second-line or add-on therapy for the management of type 2 diabetes. The guidelines do not give preference to one thiazolidinedione over another but do note a possible link between rosiglitazone and myocardial ischemia. The ADA/EASD update recommends greater caution in selecting the thiazolidinediones.

Both pioglitazone and rosiglitazone have demonstrated efficacy in improving glycemic control in type 2 diabetics and head-to-head studies have shown similar improvements in HbA_{1c} levels. Pioglitazone has demonstrated more favorable effects on lipoproteins, particularly HDL cholesterol and triglycerides, but both agents caused an increase in LDL cholesterol. Both pioglitazone and rosiglitazone carry a black box warning regarding an increased risk of congestive heart failure and a new black box warning has been added to the product labeling of rosiglitazone due to reports of a potential link to myocardial ischemic events. Due to the absence of long-term head-to-head comparisons, firm conclusions about the risk differences between these 2 agents cannot be made.

Therefore, based on the current evidence all brand products within the class reviewed are comparable to each other and to the generics and OTC products in this class and offer no significant clinical advantage over other alternatives in general use. Thiazolidinediones are beneficial to patients when other first-line agents are not tolerated, are contraindicated or do not provide adequate glycemic control.

No brand single entity thiazolidinedione is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

Dr. Woodruff noted that a paragraph in the conclusion stated that pioglitazone increased LDL, but a study summarized earlier in the review by Khan et al reported that pioglitazone decreased LDL and was concerned about this contradiction. Dr. Ferris noted that general consensus of the published studies have reported an increase in LDL with pioglitazone treatment (see meta-analysis by Bolen et al). There were no further discussions on the agents in this class. Chairman Thomas asked the P&T Committee Members to mark their ballots.

Thiazolidinediones Combination Products AHFS 682028
Manufacturer comments on behalf of these products:
Duetact® (pioglitazone and glimepiride)-Takeda

Dr. Ferris pointed out that since the previous review, Duetact® has become available. All of the agents in this class combine a thiazolidinedione with either metformin or glimepiride (a sulfonylurea). There are no generic formulations available for the combination thiazolidinediones but metformin and glimepiride are available generically.

While all of the guidelines listed include the thiazolidinediones and sulfonylureas as a treatment option for

combination therapy, only the guideline by the AACE addressed the use of fixed-dose combination products. According to the AACE guideline, for patients who are naïve to pharmacologic therapy and have an HbA_{1c} of 7%-8%, combination therapy is recommended. Regimens may include a thiazolidinedione combined with a secretagogue (or sulfonylurea) or metformin either as concurrent therapy or fixed-dose regimens.

With regards to adverse events, all thiazolidindione products carry a black box warning regarding congestive heart failure and rosiglitazone carries a black box warning regarding myocardial ischemia. Glimepiride carries a special warning for an increased risk of cardiovascular mortality. Products containing metformin carry a black box warning for lactic acidosis.

There are limited studies evaluating the safety and efficacy of fixed-dose combination products and the majority of the clinical trials were conducted with the rosiglitazone combination products. There are no head-to-head comparisons of the fixed-dose combination products. The clinical trials for the combination thiazolidinediones have demonstrated that combination therapy with two agents can help diabetic patients achieve glycemic control when monotherapy is inadequate or dose increases with one agent are not tolerated. There were 2 small studies that compared pioglitazone to rosiglitazone with add-on metformin (Derosa 2006) or glimepiride (Derosa 2004). In both of these studies, combination therapy with pioglitazone or rosiglitazone produced comparable glycemic control; however, pioglitazone produced a more favorable effect on triglycerides and lipoproteins. With regards to "Dose Simplification", a study by Vanderpoel et al noted increased adherence when patients utilized the fixed-dose combination rosiglitazone and metformin; however, clinical outcomes were not measured in this trial.

In conclusion, the combination thiazolidinedione products combine two agents with different mechanisms of action to help achieve glycemic control. In general, the fixed dose combination products were bioequivalent to concurrent administration of the separate components.

While the national and international consensus guidelines address the role of combination therapy with thiazolidinediones for the management of type 2 diabetes, only the guideline by the AACE addressed the use of fixed-dose combination products. At this time, the national and international guidelines do not give preference to one thiazolidinedione versus the other but note a possible link of rosiglitazone to cardiovascular events. A recent update to the ADA/EASD consensus guideline recommends greater caution in selecting the thiazolidinediones.

Both pioglitazone and rosiglitazone may cause or exacerbate congestive heart failure in some patients and both agents carry a black box warning regarding this adverse event. Recently this black box warning was expanded for rosiglitazone to include a potential risk for myocardial ischemia. Thus far, pioglitazone has not been associated with an increased risk of myocardial ischemic events. Glimepiride, the sulfonylurea component of the combination products, carries a special warning regarding an increased risk of cardiovascular mortality. Whether the addition of glimepiride or metformin to thiazolidinedione therapy has any impact on these risks has not yet been determined.

At this time, there is insufficient data to conclude that one brand combination thiazolidinedione is safer or more efficacious than another and offers a significant clinical advantage over other alternatives in general use. No brand combination thiazolidinedione is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred.

There were no further discussions on the agents in this class. Chairman Thomas asked the P&T Committee Members to mark their ballots.

6. RESULTS OF VOTE ANNOUNCED

Dr. Littlejohn announced the results of voting for each of the therapeutic classes. Results of voting are described in the Appendix to the minutes.

7. NEW BUSINESS

Dr. Littlejohn took a moment to share with the Committee the policy on oral presentations during the P&T Committee meetings, which states that "Oral presentations must also be limited to clinical information only and must not contain any reference to cost or general drug- or disease-specific economic information. Oral presentations must be confined to evidence-based clinical information and limited to Food and Drug Administration (FDA)-approved indications covered under Alabama Medicaid Pharmacy benefit and not contain anecdotal content. All statistics identified for discussion must be supported by noting the source from which the information was obtained." There was no other new business.

8. NEXT MEETING DATE

The next P&T Committee Meeting is scheduled for 9:00 a.m. on May 14, 2008.

9. LUNCH

The P&T Committee broke for lunch at 11:45 a.m.

10. POSITIVE ANTIPSYCHOTIC MANAGEMENT (P.A.M.) REVIEW

The meeting was reconvened at 1:15 p.m.

Dr. Littlejohn addressed the P&T Committee and informed them of the origin of the Positive Antipsychotic Management (PAM) Review. She noted that this discussion is very different from a Preferred Drug List (PDL) discussion that the Committee usually handles and that this is a prior-authorization (PA) discussion. She informed the Committee that Medicaid is currently mandated by the PDL legislation that the antipsychotic class remains excluded from review into our PDL.

To date the Agency has implemented several retrospective as well as prospective programs within the past few years relative to the antipsychotics. These programs include the retrospective Comprehensive NeuroScience program, a therapeutic duplication edit, and the maximum unit restriction program.

With all of these programs in place for several years (approximately 3-4 years), the Agency is still seeing an increasing rate of utilization in this drug class. Preliminary research in this area was done and found off-label and potential inappropriate use of these agents. Therefore, the clinical contractor was commissioned to develop a safety and efficacy clinical review for the antipsychotics.

Chairman Thomas inquired who else has been asked for comment besides the clinical contractor. Dr. Littlejohn noted that Agency has met with Mental Health prior to today to review the PAM project. Dr. Thomas stated that other physicians including child psychologists should be asked for comment, to which Dr. Littlejohn agreed.

Dr. Freeman stated that most of the time when the antipsychotics are used in young children that it is off label due to their limited indications, and also wondered why in this situation cost was included as part of the discussion. Dr. Littlejohn replied that even though this is true, information has shown that these agents are

being prescribed for individuals for whom they may not be appropriate and it is the P&T Committee's charge to review the therapeutic class for efficacy as well as safety. She continued that the origin of the P&T review was for safety and efficacy; the cost information is included for reference purposes (much like it is for the PDL discussions).

Dr. Sawyer inquired how it could be known that these agents have been used off-label. Dr. Littlejohn replied that although pharmacists do not have access to a patient's diagnosis, research was conducted that cross referenced individuals who obtained an antipsychotic drug with their medical history and documented diagnoses submitted to the Agency. Chairman Thomas stated that it is important to note that child psychiatrists have been prescribing agents such as these for a while and that no on-label option truly exists.

Dr. Littlejohn noted that included in the review, prepared by the clinical contractor, is what other state Medicaid agencies are doing with this drug class. It should be noted that in the past few years there has been a movement across the nation from excluding this drug class from the PDL, to including it into the PDL.

The Agency has met with Mental Health and they agree that this information is very concerning, and after meeting with them, the following timeline was developed:

1) On February 20, 2008, the P&T Committee will meet to determine an official recommendation to our Commissioner on the PAM proposal.
2) Beginning approximately in March, a task force will be brought together to include Mental Health as well as a group of child and adult psychiatry specialists to draft appropriate criteria, focusing on what will be available to capture in our Electronic Prior Authorization (EPA).
3) The plan is to have 2-3 task force meetings, and implement the PAM program later this year.

It was reiterated that the goal is to slowly and methodically design an appropriate program that will keep the safety and well-being of our recipients at the forefront.

Dr. Thomas stated that it is important to note that these agents are used by the physician when it is felt appropriate and that physicians are motivated by the safety of the patient and may feel that these agents help people even if these agents are being used off label. Dr. Littlejohn agreed and noted that off-label uses can be addressed in the criteria that will be prepared by the task force.

Dr. Freeman inquired why the antipsychotics were excluded from the PDL initially. Dr. Littlejohn replied that this class as well as the antiretrovirals was not included originally, and although she was not an employee of the Agency at the time of the PDL conception, her understanding was that some groups felt it was important that these agents were excluded.

Dr. Thomas asked if the task force will have access to the clinical contractor's review. Dr. Littlejohn noted the task force has not been convened as of yet and is open to the submission of names of individuals who may potentially serve on the task force, but it would be advantageous to have all clinical information available. Dr. Moon stated that the goal is for this process to be open and have experts provide input to ensure quality care. Noting no additional questions at this time, the presentation was turned over to Dr. Michael Angelini.

Dr. Angelini, an Associate Professor of Pharmacy Practice at Massachusetts College of Pharmacy and Health Sciences, was asked to present his credentials as it related to behavioral health medicine. He briefly reviewed his credentials, including his education (Masters in Clinical Psychology from Boston University, Doctor of Pharmacy from Massachusetts College of Pharmacy and Health Sciences and Board Certification in Psychiatric Pharmacy) and additional institutions where he holds academic appointments (Boston University

School of Medicine-Addictions Fellowship, Harvard Medical School, Massachusetts School of Professional Psychology and Wheelock College). He described his role at the Veterans Affairs (VA) Boston Healthcare as a clinical pharmacist with the outpatient psychiatric department and the Geriatric Research Education and Clinic Center (a Harvard Medical School affiliate) where he has medication and laboratory prescriptive authority with a scope of practice consistent with mental health, geriatrics and primary care medication treatments. At the VA Dr. Angelini's clients are from all Axis I diagnoses with a high proportion of dually diagnosed patients. Dr. Angelini mentioned he also serves as a consultant to various primary care and mental health private practices throughout New England including East Bay Center in Barrington, RI where he is a member of the pharmacy and therapeutics committee as well as serving as a scientific member of the Central Office Research Review Committee for the Department of Mental Health, Commonwealth of Massachusetts.

He then began his presentation by noting that the pharmacology of the atypical antipsychotic class of medications has overlap in certain critical therapeutic areas but each agent has uniqueness about it also.

Dopamine blockade or modulation seems to be critical for all of these medications, both the older conventional agents and the newer atypical antipsychotics. A benefit of the newer class of medications is the reduction in the potency of dopamine blockade necessary to maintain efficacy on positive symptoms. This has resulted in reductions in dopamine antagonistic adverse effects but an increase in 5-HT2 blockade effects which are generally considered metabolic in nature.

Dr. Angelini provided a quick pharmacologic review of the atypical antipsychotic class of medications and noted the similarities and differences these medications have on different neurotransmitter systems.

It was noted that a review of the safety of these medications typically occurs as a secondary measure to efficacy with serious adverse effects similar in frequency but differing in type between the agents. Although the types of side effects remain fairly constant when these agents are studied for different disease states the frequency seems to be highest in the bipolar and off label cohorts and lowest in the schizophrenia cohorts.

Dr. Angelini discussed extrapyramidal symptoms (EPS), also referred to as extrapyramidal side effects (EPSE) and noted that they are decreased in the atypical agents compared to conventional agents in this class of drugs but still exists as noted in multiple studies. Cerebral vascular accidents have been shown to occur at a greater rate with the use of antipsychotics compared to placebo when used to treat behavior, psychosis or impact cognition in the demented geriatric population as well as overall mortality. Reduction in bone mineral density occurs in patients utilizing antipsychotics as a result of increases in prolactin. Prolactin increases are an unavoidable result in potent dopamine blockade therefore a potential likely side effect with any agent in the antipsychotic class of medications. Higher levels of dopamine blockade are typically where this effect is seen yet some agents have this event at therapeutic doses. Other prolactin related adverse effects exist such as sexual dysfunction and galactorrhea.

It was noted that cognitive function in schizophrenia is typically improved with this class of medication. This is due to a reduction in psychotic symptoms and not due to a direct cognitive enhancing effect of antipsychotics. Dr. Angelini noted that metabolic risks associated with this group of medications have shown that all members of the class have a risk for weight gain but with clear delineation of high, medium and low risk with specific agents. Changes in glucose and cholesterol parameters has also been noted but at a less consistent rate than weight changes.

These medications, through there multiple pharmacologic properties, have been shown to have significant risks associated with them and need to be monitored carefully when prescribed. Other classes of medications

with less severe side effect profiles are currently managed by Alabama Medicaid and this class should not be deprived of this safety oversight.

Therefore, to ensure the safety of Alabama Medicaid recipients and to ensure appropriate use of antipsychotics in the state of Alabama, all brand, generic, and over-the-counter products within the antipsychotics class should be managed through the electronic prior-authorization process, and off-label use should be managed through the medical justification portion of the prior-authorization process.

In an effort to follow evidence-based national guidelines and to ensure the appropriate and safe utilization of antipsychotics, Alabama Medicaid should place all antipsychotics in the Electronic Prior-Authorization Program. Criteria should be drafted to ensure all patients with a diagnosis of bipolar disease, schizoaffective disease, and schizophrenia are able to immediately obtain these agents at the point-of-sale through electronic prior authorization based on their diagnosis. Additional criteria should be drafted so that off-label use is managed through the medical justification portion of the prior-authorization process.

Dr. Woodruff inquired if there were any more recent studies published on the drug interactions associated with these agents. Dr. Gagnon replied that there is not a substantial amount of published drug interaction studies and referred the committee to an earlier section of the document where the drug interactions associated with these agents are summarized.

Dr. Freeman inquired if there are any other categories of drugs that may potentially be restricted by Medicaid in the future. Dr. Littlejohn clarified that these agents would be immediately available to patients who meet the appropriate criteria (as defined by the workgroup of experts and supported by evidence-based medication); also there are no restrictions on drugs based on the prescriber type.

Ms. Faulk inquired if this would help with children who are brought to multiple prescibers. Dr. Freeman replied that she did not feel this was an issue.

Mr. Main raised concern for the quality of care of patients who are already stabilized on these agents. Dr. Littlejohn replied that stable therapy could be addressed by the workgroup and the criteria.

Chairman Thomas stated he would like to table this topic until after the task force meets. Dr. Littlejohn clarified that as the recommendation is written the task force would be convened if the P&T Committee voted to move forward with the recommendation.

An amendment was made by Mr. Main and Dr. Freeman and seconded by Ms. Boston recommending to table discussion until the task force meets; after that time the task force's recommendations will be brought back to the P&T Committee. Dr. Littlejohn clarified the recommendation and noted that the P&T recommendations will go to the Commissioner for final approval.

There were no further discussions on the agents in this class. Chairman Thomas asked the P&T Committee Members to mark their ballots.

11. ADJOURN

The meeting was adjourned at 3:00 p.m.

Appendix

RESULTS OF THE BALLOTING
Alabama Medicaid Agency
Pharmacy and Therapeutics Committee
February 20, 2008

A. **Recommendation**: No brand estrogen is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

Amendment: None

Vote: Unanimous to approve as recommended

Medical Director	☑	Approve	☐	Approve as amended	☐	Disapprove	☐ No action
Deputy Commissioner	☑	Approve	☐	Approve as amended	☐	Disapprove	☐ No action
Commissioner	☑	Approve	☐	Approve as amended	☐	Disapprove	☐ No action

B. **Recommendation**: No brand α-glucosidase inhibitor is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

Amendment: None

Vote: Unanimous to approve as recommended

Medical Director	☑	Approve	☐	Approve as amended	☐	Disapprove	☐ No action
Deputy Commissioner	☑	Approve	☐	Approve as amended	☐	Disapprove	☐ No action
Commissioner	☑	Approve	☐	Approve as amended	☐	Disapprove	☐ No action

C. **Recommendation**: No brand amylinomimetic is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred agents.

Amendment: None

Vote: Unanimous to approve as recommended

Medical Director	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action
Deputy Commissioner	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action
Commissioner	☒	Approve	☐	Approve as amended	☐	Disapprove	☐	No action

D. **Recommendation**: No brand biguanide is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred.

Amendment: None

Vote: Unanimous to approve as recommended

Medical Director	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action
Deputy Commissioner	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action
Commissioner	☒	Approve	☐	Approve as amended	☐	Disapprove	☐	No action

E. **Recommendation**: No brand single entity dipeptidyl peptidase-4 (DPP-4) inhibitor is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

Amendment: None

Vote: Unanimous to approve as recommended

Medical Director	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action
Deputy Commissioner	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action
Commissioner	☒	Approve	☐	Approve as amended	☐	Disapprove	☐	No action

F. **Recommendation**: No brand combination dipeptidyl peptidase-4 (DPP-4) inhibitor is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

Amendment: None

Vote: Unanimous to approve as recommended

Medical Director	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action
Deputy Commissioner	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action
Commissioner	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action

G. **Recommendation**: No brand incretin mimetic is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred agents.

Amendment: None

Vote: Unanimous to approve as recommended

Medical Director	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action
Deputy Commissioner	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action
Commissioner	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action

H. **Recommendation**: Alabama Medicaid should work with manufacturers on cost proposals so that at least one brand rapid-acting insulin analog is selected as a preferred agent.

Alabama Medicaid should work with manufacturers on cost proposals so that at least one brand long-acting insulin analog is selected as a preferred agent.

No brand insulin, with the exception of the rapid- and long-acting insulin analogs, is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands

Amendment: None

Vote: Unanimous to approve as recommended

Medical Director	☑	Approve	☐	Approve as amended	☐	Disapprove	☐ No action
Deputy Commissioner	☑	Approve	☐	Approve as amended	☐	Disapprove	☐ No action
Commissioner	☑	Approve	☐	Approve as amended	☐	Disapprove	☐ No action

I. **Recommendation**: No brand meglitinide is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

Amendment: None

Vote: Unanimous to approve as recommended

Medical Director	☑	Approve	☐	Approve as amended	☐	Disapprove	☐ No action
Deputy Commissioner	☑	Approve	☐	Approve as amended	☐	Disapprove	☐ No action
Commissioner	☑	Approve	☐	Approve as amended	☐	Disapprove	☐ No action

J. **Recommendation**: No brand single entity sulfonylurea is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

Amendment: None

Vote: Unanimous to approve as recommended

R Moore MD	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action
Medical Director								
Kathy Hall	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action
Deputy Commissioner								
Carol Steckel	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action
Commissioner								

K. **Recommendation**: No brand combination sulfonylurea is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

Amendment: None

Vote: Unanimous to approve as recommended

R Moore MD	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action
Medical Director								
Kathy Hall	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action
Deputy Commissioner								
Carol Steckel	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action
Commissioner								

L. **Recommendation**: No brand single entity thiazolidinedione is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

Amendment: None

Vote: Unanimous to approve as recommended

R Moore MD	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action
Medical Director								
Kathy Hall	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action
Deputy Commissioner								
Carol Steckel	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action
Commissioner								

M. **Recommendation**: No brand combination thiazolidinedione is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

Amendment: None

Vote: Unanimous to approve as recommended

Medical Director	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action
Deputy Commissioner	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action
Commissioner	☑	Approve	☐	Approve as amended	☐	Disapprove	☐	No action

N. **Recommendation**: In an effort to follow evidence-based national guidelines and to ensure the appropriate and safe utilization of antipsychotics, Alabama Medicaid should place all antipsychotics in the Electronic Prior-Authorization Program. Criteria should be drafted to ensure all patients with an appropriate diagnosis are able to immediately obtain these agents at the point-of-sale through electronic prior authorization based on their diagnosis. Additional criteria should be drafted so that off-label use is managed through the medical justification portion of the prior-authorization process.

Amendment: To table recommendation until the task force meets and makes their recommendations for the criteria and the task force's recommendations will be brought back to the P&T Committee.

Vote:

Medical Director	☐	Approve	☑	Approve as amended	☐	Disapprove	☐	No action
Deputy Commissioner	☐	Approve	☑	Approve as amended	☐	Disapprove	☐	No action
Commissioner	☐	Approve	☑	Approve as amended	☐	Disapprove	☐	No action

Respectfully submitted,

2/20/08

James Gagnon, Pharm.D. Date